CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-718/S-010

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-718/S-010
Applicant: COR Therapeutics, Inc.
Drug Name: INTEGRILIN (eptifibatide) Injection
Indication: Percutaneous coronary intervention with stent implantation
Documents Reviewed: Vols 38.6, 38.7, DSMC meeting minutes, SAS data sets

Key Statistical Issue(s): Change early stopping rule in the interim and the trial stopped at the 2nd interim analysis

1. INTRODUCTION

In this NDA supplement, the sponsor submitted the findings of ESPIRIT trial to support use of integrilin in patients undergoing non-acute percutaneous coronary intervention with stent implantation. This is the subject of this review. Tables 1, 2, 3a, 3b, 4a and 4b summarize the results of the interim analyses provided in the DSMC meeting minutes. For the final analysis database, this reviewer's analyses give results very similar to the sponsor's results. They are reported in Tables 5-12. In addition, this reviewer performed a number of simulation studies to give a ballpark assessment for the true p-value of the primary efficacy endpoint (see Table 13).

2. OVERVIEW OF ESPIRIT TRIAL FINDINGS

This multi-center, randomized, double-blind, parallel-group, placebo-controlled trial was designed to evaluate the efficacy and safety of eptifibatide (an initial bolus of 180 μg/kg, immediately followed by a 2.0 μg/kg-min infusion, and a second bolus of 180 μg/kg 10 minutes later) as an adjunct to non-emergent percutaneous coronary intervention (PCI) with stent implantation. For patients with a baseline serum creatinine >2.0 and ≤4.0 mg/dL, the infusion dose was adjusted to 1.0 μg/kg-min. The infusion was to continue until hospital discharge or up to a maximum of 18-24 hours, whichever occurred first. Patients could be switched by treating physicians to open-label eptifibatide therapy through a bail-out kit to be administered as a single bolus at a dose of 180 μg/kg if it were thought to be in the best interest of the patients.

All patients received concomitant aspirin and heparin. The readers are referred to the medical review for details. Ticlopidine or clopidogrel were not permitted within 15 days before the PCI procedure on the day of the procedure, but administration of a loading dose of ticlopidine or clopidogrel was permitted. Adjunctive anti-platelet therapy with either ticlopidine 250 mg bid or clopidogrel 75 mg qd was encouraged after stent implantation.

The study drug could be terminated prematurely due to an adverse event, significant bleeding, or if the physician deemed it necessary.

Blinding

According to the study report, each injection and infusion vial was over-labeled with double-blind labels. The matching placebo was indistinguishable from eptifibatide. The unblinding procedure appeared to be quite standard.

Efficacy Endpoints

The primary efficacy endpoint was the composite of death, MI (myocardial infarction), UTVR (urgent target vessel revascularization), and thrombotic 'bail-out' GP IIb/IIIa inhibitor therapy within 48 hours. The key secondary endpoint was the composite of death, MI, and UTVR within 30 days. Other secondary endpoints are composites from similar kinds of components of these two endpoints at different time points. Procedures were in place for adjudicating the clinical events; see the medical review for details.

Planned Statistical Methods

Analyses were to be performed on the 'all randomized' (intent-to-treat) patients, i.e., the patients who received any study medication regardless of whether PCI or coronary stenting was performed. Analyses were also to be performed in the population of patients actually receiving both study medication and coronary stents. Each of the endpoints was to be analyzed via the use of a chi-square test without continuity correction. There was no plan for making statistical adjustment for testing the two endpoints. The implication is that statistical significance on the result of the key secondary efficacy endpoint will be argued only when statistical significance on the primary endpoint is conclusive.

Sample Size Determination and Re-estimation

A sample size of 1200 per treatment group was planned to detect a 33% relative reduction in the percentage of patients with the key secondary endpoint at 5% level of significance and with power 86%, assuming a placebo event rate of 11.0%. This sample size would also have 90% power to detect a 33% relative reduction in the percentage of patients with the primary endpoint, assuming a placebo event rate of 12.0%. There was a plan to conduct a blinded sample size assessment by the sponsor after DCRI received and entered data from the 30-day follow-up CRFs for approximately 1700 patients in total. This sample size re-estimation was to be based on an assumed 33% relative reduction and the observed pooled event rates for both the primary and key secondary endpoints. According to the study report, the re-estimation did not occur.

Interim Analysis Plan

Aside from the monthly monitoring of serious adverse events by the chairperson, there were two protocol-specified safety reviews to be held by the DSMC members via teleconference, the first after 500 patients had been enrolled and the second after 1400 patients had been enrolled. During the safety review, the committee would minimally review the serious adverse event, including the incidence of thrombocytopenia and major bleeds.

There were no planned interim efficacy analyses since it was thought that based on enrollment projections the study patients would be completely enrolled before sufficient data could be obtained for making any early stopping decision. However, there was the provision to allow the DSMC to review efficacy data and the protocol defined an alpha level of 0.0001 for each interim look at efficacy data and the final analysis would be conducted at the significance level of $\alpha = 0.05 - k(0.0001)$, where k is the number of times that the DSMC sees efficacy results by treatment group.

According to the study report, all data presentations and analyses required by the DSMC were performed by two statisticians, Dr. Hasselblad and Ms. Cindy Pacchiana, at Duke Clinical Research Institute to keep the sponsor completely blinded.

EFFICACY RESULTS

The ESPIRIT trial was stopped prematurely by the DSMC for overwhelming treatment difference on the efficacy endpoints.

Two interim efficacy analyses were performed by DCRI, at the request of DSMC. The committee minutes noted that the DSMC would

need to examine interim efficacy data because of much slower enrollment rate than anticipated and much more rapid data collection in order to assure investigators that their clinical obligation to deliver appropriate care was met. Thus, during the second safety review held December 16, 1999, the committee considered examining efficacy data with intention of stopping the trial early in case of overwhelming treatment benefit. The committee decided to meet on December 21, 1999 to review the overall blinded event rate and hypothetical treatment differences needed to meet the protocol-defined level of α=0.0001.

At the December 21, 1999 meeting, the committee decided to plan a formal interim analysis to examine efficacy data. The ability of meet the 0.0001 alpha level was discussed. It was decided that two tables, one with 48-hour data and one with 30-day data, would be reviewed and clinical judgement would need to be used in making a decision if a robust treatment effect were seen that did not meet this 0.0001 level. Dr. Fisher noted that based on these tables it would take a 60% reduction in order to reach the pre-specified 0.0001 level. In addition, according to the 12/21/99 DSMC meeting minutes, Dr. Fisher stated that he was concerned that the committee would have a difficult decision to make if p = 0.005. The tables to be prepared would include the primary endpoint and key secondary endpoints, as well as the components of these endpoints. What constitutes a 'robust' treatment effect was not described. Though the intention to review efficacy data was conveyed to the Sponsor and Executive Committee, the specifics of the interim analysis including their intention to modify the protocol stopping rules were not disclosed. The Sponsor did not submit a protocol amendment. The committee felt reasonable to proceed with an interim analysis since the treatment would have potential of an approximately 50% reduction in events as observed in the EPISTENT trial. A formal interim efficacy analysis was planned to take place in January, 2000.

1st Interim Analysis

According to the meeting minutes, at the January 12, 1999 meeting, the efficacy results were first presented as summarized

Table 1. Efficacy endpoints at 48 hours - 1st interim analysis

	Treatment A (N=741)	Treatment B (N=743)	p-value*
Death/MI/UTVR/TBO	46 (6.2%)	76 (10.2%)	0.0048
Death/MI/UTVR	40 (5.4%)	65 (8.7%)	0.0118
Death/MI	36 (4.9%)	64 (8.6%)	0.0039
Death	1 (0.1%)	2 (0.3%)	0.56
MI	36 (4.9%)	62 (8.3%)	0.0069
UTVR	5 (0.7%)	6 (0.8%)	0.77

Urgent PCI	1 (0.1%)	5 (0.7%)	
Urgent CABG	4 (0.5%)	1 (0.1%)	
TBO	8 (1.1%)	17 (2.3%)	0.071

*p-value from an unadjusted conventional chi-square test
This table excerpted from Table 9 in the 01/12/00 DSMC meeting minutes

in the following tables. The MI cases were further discussed. It appeared that there would be a significant treatment difference on MI and other composite endpoints.

Table 2. Efficacy endpoints at 30 days (only including patients with complete 30 day follow-up) - 1st interim analysis

	Treatment A (N=551)	Treatment B (N=553)	p-value*
Death/MI/UTVR	33 (6.0%)	57 (10.3%)	0.0090
Death/MI	30 (5.5%)	56 (10.2%)	0.0038
Death	2 (0.4%)	5 (0.9%)	0.26
MI	30 (5.4%)	51 (9.2%)	0.016
UTVR	6 (1.1%)	6 (1.1%)	0.995
Urgent PCI	3 (0.5%)	5 (0.9%)	
Urgent CABG	3 (0.5%)	1 (0.2%)	

*p-value from an unadjusted conventional chi-square test
This table excerpted from Table 9 in the 01/12/00 DSMC meeting minutes

The DSMC concluded that analysis of the primary endpoint did not reach the overall level of 0.0001 but they pointed out that data discrepancies existed that could lead to different interpretations and the majority of cases needed to be reviewed by the CEC.

The extreme conservatism of 0.0001 alpha level was extensively discussed. Dr. Hasselblad reviewed his conditional power calculations for a second look at efficacy using different cumulative alpha levels (0.0002 and 0.001). The calculations indicated that there was a high probability (>99%) that the study would have a positive outcome ($p<0.05$) if the study were taken to full enrollment assuming the observed effectiveness trend persisted. After noting that there did not appear to be any significant safety issues, the DSMC decided to plan a second interim analysis for efficacy. A discussion ensued on appropriate stopping rules. It was decided that the composite endpoint of death/MI at 48 hours should be used as the primary consideration for the efficacy look since death and MI constitute irreversible clinical injury. It was suggested by Dr. Cannon (DSMC Chair) and later agreed by Dr. Fisher (DSMC Statistician) that this second look at the efficacy data be planned with $\alpha=0.005$ to be more in line with stopping rules used for similar

studies[1]. ***This reviewer noted that the selected alpha of 0.005 is very close to the nominal p-values seen in MI and the composite endpoints (see Table 2). Were these observed p-values a part of guidance in selecting the 0.005 alpha level for the 2nd interim analysis? This issue will be discussed in Section 3.***

According to the study report, the Sponsor was notified by phone of the DSMC's intent to analyze efficacy data in early February without any other details of the DSMC's deliberations.

2nd Interim Analysis

At this meeting held February 3, 2000, the DSMC recommended to terminate the trial prematurely for overwhelming efficacy.

The meeting appeared to begin with establishing the criteria for stopping the trial early by the committee members and then the efficacy data were reviewed. Dr. Kerry Lee, a DCRI statistician, was invited to participate in this discussion. Dr. Cannon reiterated that the selection of the 0.005 alpha level for this interim analysis was based on the preponderance of evidence that GP IIb/IIIa are effective for this indication and there was precedent for this (CAPTURE trial stopped early based on an alpha level of 0.007). After discussion, the committee agreed upon the following two criteria for stopping the trial early based on efficacy.

1) Alpha level of 0.005 for the test of treatment difference on death/MI at 48 hours,
2) Consistency among the other endpoints, notably the primary composite endpoint at 48 hours and 30 days, and death/MI at 30 days.

Again, there was no description about what constitutes consistency.

Safety tables appeared to have been reviewed first. The committee agreed that the two treatment groups looked comparable and there were no outstanding safety concerns with respect to the serious adverse events.

The sealed envelops containing unblinded efficacy data were then opened. The results are summarized in the following tables. The

[1] Dr. Cannon reviewed the two other GP IIb/IIIa inhibitor trials that were terminated prematurely as a means of finding guidance: 1) CAPTURE trial, which had 2 planned efficacy looks at alpha = 0.0001 for the first look and alpha = 0.001 for the second look. CAPTURE performed one unplanned look using alpha = 0.0072 which is the basis of early termination of the trial for reasons of overwhelming efficacy. 2) In the EPILOG trial, an alpha = 0.001 was used when the trial was stopped prematurely for efficacy.

two stopping criteria were met according to the committee's assessment. In addition, Dr. Hasselblad noted that the predictive power using alpha = 0.05 at 2400 patients was 99.6% assuming the current trend persists. The committee unanimously agreed that the trial be stopped based on overwhelming efficacy without safety concerns.

Table 3a. Efficacy endpoints at 48 hours - 2nd interim analysis

	Treatment A (N=879)	Treatment B (N=879)	p-value*
Death/MI/UTVR/TBO	55 (6.3%)	90 (10.2%)	0.0024
Death/MI/UTVR	47 (5.3%)	77 (8.8%)	0.0052
Death/MI	43 (4.9%)	76 (8.6%)	0.0017
Death	0?	2 (0.2%)	0.16
MI	43 (4.9%)	74 (8.4%)	0.0030
UTVR Urgent PCI Urgent CABG	5 (0.6%) 1 (0.1%) 4 (0.5%)	6 (0.7%) 5 (0.6%) 1 (0.1%)	0.76
TBO	10 (1.1%)	19 (2.2%)	0.092

*p-value from an unadjusted conventional chi-square test
? this is a questionable number since the 1st interim analysis had already seen a death
This table excerpted from Table 9a in the 02/03/00 DSMC meeting minutes

Table 3b. Investigator efficacy results at 48 hours - 2nd interim analysis

	Treatment A (N=879)	Treatment B (N=879)	p-value*
Death/MI/UTVR/TBO	39 (4.4%)	50 (5.7%)	0.23
Death/MI/UTVR	31 (3.5%)	35 (4.0%)	0.62
Death/MI	26 (3.0%)	32 (3.6%)	0.42
Death	0?	2 (0.2%)	0.16
MI	26 (3.0%)	30 (3.4%)	0.59
UTVR Urgent PCI Urgent CABG	6 (0.7%) 1 (0.1%) 5 (0.6%)	8 (0.9%) 6 (0.7%) 2 (0.2%)	0.59
TBO	9 (1.0%)	21 (2.4%)	0.027

*p-value from an unadjusted conventional chi-square test
? this is a questionable number since the 1st interim analysis had already seen a death
This table excerpted from Table 9b in the 02/03/00 DSMC meeting minutes

Table 4a. Efficacy endpoints at 30 days - 2nd interim analysis

	Treatment A (N=687)	Treatment B (N=697)	p-value*
Death/MI/UTVR	40 (5.8%)	70 (10.0%)	0.0037
Death/MI	36 (5.2%)	69 (9.9%)	0.0011
Death	1 (0.1%)	6 (0.9%)	0.0274

MI	36 (5.2%)	64 (9.2%)	0.0046
UTVR	7 (1.0%)	8 (1.1%)	0.82
Urgent PCI	3 (0.4%)	6 (0.9%)	
Urgent CABG	4 (0.6%)	3 (0.4%)	

*p-value from an unadjusted conventional chi-square test
This table excerpted from Table 10a in the 02/03/00 DSMC meeting minutes

Table 4b. Investigator efficacy results at 30 days - 2nd interim analysis

	Treatment A (N=687)	Treatment B (N=697)	p-value*
Death/MI/UTVR	28 (4.1%)	34 (4.9%)	0.47
Death/MI	22 (3.2%)	31 (4.4%)	0.23
Death	1 (0.1%)	6 (0.9%)	0.061
MI	22 (3.2%)	26 (3.7%)	0.59
UTVR	8 (1.2%)	10 (1.4%)	0.66
Urgent PCI	3 (0.4%)	8 (1.1%)	
Urgent CABG	5 (0.7%)	4 (0.6%)	

*p-value from an unadjusted conventional chi-square test
This table excerpted from Table 10b in the 02/03/00 DSMC meeting minutes

Final analysis - 2nd Interim Analysis after data are locked

A total of 2,064 patients (1,024 placebo patients and 1,040 eptifibatide patients) were randomized. About 96% of the patients received only study drug without bail-out and 96% of patients received stent placement. There was only one patient in each group who was lost to follow-up for 30-day assessment. About 10% of the patients had study drug terminated early by study design, primarily because of early discharge from the hospital. In addition, there were about 12% of the patients who had study drug terminated early not by study design. The most common reason was discontinuation due to a bleeding adverse event, particularly in the eptifibatide group (4.6%) as compared to the placebo group (0.9%). The most common category checked on the case report form was 'other reason', about 6% in each treatment group. There were very few protocol deviations and very few patients with the study medication being unblinded. Fifty patients received study drug out of sequence due to errors at the investigational site. However, no patients received an incorrect assigned treatment.

The final analysis was performed on all the 2,064 patients as an intent-to-treat population using the final locked database (note: the planned total sample size is 2,400 and the study was terminated prematurely).

The two treatment groups were similar with respect to baseline characteristics (Table 5) and concomitant therapy at baseline and in the immediate post-PCI period (Table 6).

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Table 5. Baseline characteristics

	Placebo (N=1024)	Eptifibatide (N=1040)
Age (mean yrs ± sd)	62±11	62±11
Gender		
Male	742 (73%)	760 (73%)
Female	282 (27%)	280 (27%)
Weight (mean kg ± sd)	87±18	85±18
Ethnicity		
Caucasian	930 (91%)	927 (89%)
Black	43 (4%)	52 (5%)
Asian	11 (1%)	16 (2%)
Hispanic	21 (2%)	21 (2%)
Native American	2 (0.2%)	6 (0.6%)
Asiatic Indian	15 (2%)	12 (1%)
Other	2 (0.2%)	6 (0.6%)
Country		
USA	759 (74%)	772 (74%)
Canada	265 (26%)	268 (26%)
Hypertension	605 (59%)	608 (59%)
Diabetes	211 (21%)	208 (20%)
Hypercholesterolemia	599 (59%)	600 (58%)
Cigarette Smoking		
Current	228 (23%)	250 (24%)
Former	474 (47%)	498 (48%)
Previous MI	321 (31%)	331 (32%)
Previous PCI	246 (24%)	237 (23%)
Previous CABG	105 (10%)	106 (10%)
Previous stroke	45 (4%)	44 (4%)
Peripheral vascular disease	71 (7%)	66 (6%)
Angiographic findings@		
% Stenosis of index lesion	87%	87%
TIMI Grade Flow		
0	47 (5%)	34 (3%)
1	22 (2%)	33 (3%)
2	89 (9%)	86 (9%)
3	804 (84%)	842 (85%)
Target vessel location		
LAD	396 (39%)	404 (39%)
RCA	344 (34%)	364 (35%)
LCX	275 (27%)	265 (26%)
Left Main	7 (0.7%)	6 (0.6%)
Thrombus present in index lesion	41 (4%)	47 (5%)

@ Not all patients had data

Table 6. Concomitant therapy at baseline and in the immediate post-PCI period

	Placebo (N=1024)	Eptifibatide (N=1040)
Aspirin	1021 (99.7%)	1035 (99.7%)
Ticlodipine	27 (3%)	28 (3%)
Clopidogrel	982 (96%)	991 (95%)
Heparin use for ACS	283 (28%)	294 (28%)
Heparin use for PCI	62 (6%)	53 (5%)

Analysis of Primary and Key Secondary Efficacy Endpoints

The primary efficacy endpoint was a composite of the events of death, MI, UTVR and TBO at 48 hours. The key secondary efficacy endpoint was a composite of the events of death, MI and UTVR at 30 days. The results based on CEC adjudicated events are given in Table 7. There was a 37% relative reduction in the primary endpoint in patients treated with eptifibatide compared to placebo-treated patients (nominal p = 0.0015). Eptifibatide gave a 35% reduction in the incidence of the key secondary endpoint (nominal p = 0.0034). Table 8 shows that eptifibatide appeared to give a slightly larger effect at 12 hours and then the effect in terms of % risk reduction stabilized up to 30 days.

Table 7. Primary endpoint and key secondary endpoint (CEC adjudicated)

	Placebo (N=1024)	Eptifibatide (N=1040)	Relative risk (95% CI)	p*
Primary endpoint				
Death/MI/UTVR/TBO 48 hrs	**108 (10.5%)**	**69 (6.6%)**	**0.63 (0.47, 0.84)**	**0.0015**
Death	2 (0.2%)	1 (0.1%)	0.49 (0.04, 5.42)	0.55
MI	92 (9.0%)	56 (5.4%)	0.60 (0.43, 0.83)	0.0015
UTVR	10 (1.0%)	6 (0.6%)	0.60 (0.22, 1.62)	0.30
TBO	22 (2.1%)	10 (1.0%)	0.45 (0.22, 0.94)	0.029
Key secondary endpoint				
Death/MI/UTVR 30 days	**107 (10.4%)**	**71 (6.8%)**	**0.65 (0.49, 0.87)**	**0.0034**
Death	6 (0.6%)	4 (0.4%)	0.66 (0.19, 2.32)	0.51
MI	99 (9.7%)	64 (6.2%)	0.64 (0.47, 0.86)	0.0031
UTVR	17 (1.7%)	11 (1.1%)	0.64 (0.30, 1.35)	0.24

* nominal p-value (not adjusted for interim analyses)

Table 8. Primary endpoint and key secondary endpoint (CEC adjudicated) over time

	Placebo (N=1024)	Eptifibatide (N=1040)	Relative risk	p*
Death/MI/UTVR/TBO				
12 hours	65 (6.3%)	37 (3.6%)	0.56	0.0035
24 hours	105 (10.3%)	69 (6.6%)	0.65	0.0031
48 hours	108 (10.5%)	69 (6.6%)	0.63	0.0015
7 days	114 (11.1%)	75 (7.2%)	0.65	0.0020
30 days	120 (11.7%)	78 (7.5%)	0.64	0.0011
Death/MI/UTVR				
12 hours	50 (4.9%)	28 (2.7%)	0.55	0.0091
24 hours	92 (9.0%)	62 (6.0%)	0.66	0.0090
48 hours	95 (9.3%)	62 (6.0%)	0.64	0.0045
7 days	101 (9.9%)	68 (6.5%)	0.66	0.0059
30 days	107 (10.4%)	71 (6.8%)	0.65	0.0034

* nominal p-value

The most severe event for each patient was also analyzed. According to severity, the components of each composite endpoint were in the order of death > nonfatal MI > UTVR without MI > TBO without MI or UTVR. The results suggest that most of the eptifibatide effect was seen in a reduction of nonfatal MI (38%-40% reductions at 48 hours and 30 days).

Investigators' Assessment of Primary and Key Secondary endpoints

The principal investigators also assessed whether patients had experienced an endpoint event. Table 9 summarizes the results of their assessment at 24 and 48 hours and 7 and 30 days as pre-specified secondary endpoints. Clearly, the CEC adjudication process added substantially more events to each treatment group and % risk reduction was about twice as large in the CEC adjudication as compared to the investigators' assessment.

Table 9. Primary endpoint and key secondary endpoint (Investigators' assessed) over time

	Placebo (N=1024)	Eptifibatide (N=1040)	Relative risk	p*
Death/MI/UTVR/TBO				
24 hours	56 (5.5%)	50 (4.8%)	0.88	0.50
48 hours	64 (6.3%)	51 (4.9%)	0.78	0.18
7 days	71 (6.9%)	57 (5.5%)	0.79	0.17
30 days	77 (7.5%)	60 (5.8%)	0.77	0.11
Death/MI/UTVR				
24 hours	41 (4.0%)	41 (3.9%)	0.99	0.94
48 hours	49 (4.8%)	42 (4.0%)	0.84	0.41
7 days	56 (5.5%)	48 (4.6%)	0.84	0.38
30 days	63 (6.2%)	51 (4.9%)	0.80	0.21

* nominal p-value

According to the study report, the primary category of discordance in the results between the CEC and the PIs was in MI. There were 88 MI events identified by the CEC but not by the PIs. The sponsor explained that the most likely explanation of this discrepancy is the fact that the PIs did not have the CK-MB values from the CEC Core Laboratory during the course of the study and in many cases the PI only obtained local CK-MB values from patients after they manifested symptoms. There were 20 MI cases identified by the PIs but refuted by the CEC.

Other Secondary Endpoints

The results of death/MI appeared to be consistent with the results of the primary endpoint and the key secondary endpoint over time; as seen in Table 10.

Table 10. Other secondary endpoints

	Placebo (N=1024)	Eptifibatide (N=1040)	Relative risk	p*
Death/MI				
24 hours	91 (8.9%)	57 (5.5%)	0.62	0.0027
48 hours	94 (9.2%)	57 (5.5%)	0.60	0.0013
7 days	99 (9.7%)	63 (6.1%)	0.63	0.0023
30 days	104 (10.2%)	66 (6.3%)	0.62	0.0016
'Bail-Out' for any reason	43 (4.2%)	35 (3.4%)	0.80	0.32
'Bail-Out' due to Thrombotic complications	22 (2.1%)	10 (1.0%)	0.45	0.029
Post-PCI abrupt closure	6/1015 (0.6%)	1/1025 (0.1%)	0.16	0.057

* nominal p-value

Multicenter Studies

There was no evidence for heterogeneity of the eptifibatide effect between US and Canada (Breslow-Day test for heterogeneity of odds ratio gives p > 0.74, Table 11). Most of the centers had a very small number of patients. The sponsor examined the 12 sites that had at least 50 patients and found no evidence of striking heterogeneity of the eptifibatide effect, as shown in the sponsor's Table 14.2.28 in Volume 38.7.

Table 11. By Country results

	Placebo N # (%)	Eptifibatide N # (%)	Odds ratio (95% CI)	p-value
Primary Endpoint (Death/MI/UTVR/TBO at 48 hours)				
US	759 89 (11.7%)	772 56 (7.3%)	0.59 (0.42, 0.84)	0.0028
Canada	265 19 (7.2%)	268 13 (4.9%)	0.66 (0.32, 1.37)	0.26
Key Secondary Endpoint (Death/MI/UTVR at 30 days)				
US	759 89 (11.7%)	772 58 (7.5%)	0.61 (0.43, 0.87)	0.0051
Canada	265 18 (6.8%)	268 13 (4.9%)	0.70 (0.34, 1.46)	0.34

Subgroup Results

There was no evidence that a subgroup showed no effect of eptifibatide or a reversed trend.

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Table 12. Primary endpoint (death/MI/UTVR/TBO at 48 hours) by subgroups

	Placebo N	# (%)	Eptifibatide N	# (%)	Odds ratio (95% CI)
Age					
< 65 years	580	47 (8.1%)	592	40 (6.8%)	0.82 (0.53, 1.27)
≥ 65 years	444	61 (13.7%)	448	29 (6.5%)	0.43 (0.27, 0.69)
Gender					
Male	742	67 (9.0%)	760	52 (6.8%)	0.74 (0.51, 1.08)
Female	282	41 (14.5%)	280	17 (6.1%)	0.38 (0.21, 0.69)
Race					
Caucasian	930	97 (10.4%)	927	61 (6.6%)	0.60 (0.43, 0.84)
Others	94	11 (11.7%)	113	8 (7.1%)	0.57 (0.22, 1.49)
Weight					
≤ 75 kg	272	40 (14.7%)	299	22 (7.4%)	0.46 (0.27, 0.80)
> 75 to < 90 kg	356	35 (9.8%)	367	25 (6.8%)	0.67 (0.39, 1.15)
≥ 90 kg	396	33 (8.3%)	374	22 (5.9%)	0.69 (0.39, 1.20)
Diabetic					
Yes	211	14 (6.6%)	208	8 (3.8%)	0.56 (0.23, 1.37)
No	813	94 (11.6%)	832	61 (7.3%)	0.60 (0.43, 0.85)
Cigarette Smoking					
Current smoker	228	24 (10.5%)	250	14 (5.6%)	0.50 (0.25, 1.00)
Former smoker	474	46 (9.7%)	498	38 (7.6%)	0.77 (0.49, 1.21)
Never smoked	311	36 (11.6%)	285	17 (6.0%)	0.48 (0.27, 0.88)
Hypertension					
Yes	605	65 (10.7%)	608	43 (7.1%)	0.63 (0.42, 0.95)
No	418	43 (10.3%)	432	26 (6.0%)	0.56 (0.34, 0.93)
Hypercholesterolemia					
Yes	599	57 (9.5%)	600	36 (6.0%)	0.61 (0.39, 0.94)
No	424	51 (12.0%)	440	33 (7.5%)	0.59 (0.37, 0.94)
History of MI					
Yes	321	33 (10.3%)	331	26 (7.9%)	0.74 (0.43, 1.27)
No	703	75 (10.7%)	709	43 (6.1%)	0.54 (0.37, 0.80)
Previous PCI					
Yes	246	30 (12.2%)	237	23 (9.7%)	0.77 (0.44, 1.38)
No	778	78 (10.0%)	803	46 (5.7%)	0.55 (0.37, 0.80)
Previous CABG					
Yes	105	9 (8.6%)	106	5 (4.7%)	0.53 (0.17, 1.63)
No	919	99 (10.8%)	934	64 (6.9%)	0.61 (0.44, 0.85)
History of PVD					
Yes	71	7 (9.9%)	66	4 (6.1%)	0.59 (0.16, 2.12)
No	953	101 (10.6%)	974	65 (6.7%)	0.60 (0.44, 0.84)
History of Stroke					
Yes	45	3 (6.7%)	44	1 (2.3%)	0.33 (0.03, 3.26)
No	979	105 (10.7%)	996	68 (6.8%)	0.61 (0.44, 0.84)

3. REVIEWER'S EVALUATION

The CEC-adjudicated results of primary endpoints, key secondary endpoint and death/MI at 12 hours, 48 hours, 7 days and 30 days gave p-values in the order between 0.01 and 0.001, based on the final database after the trial stopped at the 2nd interim analysis. The conditional power assessment performed by Dr. Hasselblad also supported the high likelihood that the study would have a positive outcome if the study continued to the end. The sample size of this interim analysis is about 73% of the planned sample size. The sample size of the analysis on the final database is about 86% of the planned sample size. There was no subgroup that observed a reversed trend or no trend against eptifibatide. Thus, this reviewer would conclude that this trial provides statistical evidence in support of the beneficial effect of eptifibatide in the intended patient population.

It is obviously difficult to quantify the strength of statistical evidence against the null hypothesis of no effect of eptifibatide in terms of the p-value for the primary endpoint. For one reason, the alpha spending rule was modified (i.e., nominal α level was changed from 0.0001 to 0.005 for the 2nd interim analysis) after the results of the 1st formal interim analysis for efficacy were assessed. The DSMB meeting minutes reported that the modification was based on the evidence and conduct of CAPTURE trial (see the footnote of page 5). ***This reviewer noted that the selected alpha of 0.005 is very close to the nominal p-values seen in MI and the composite endpoints seen in the 1st interim analysis. According to the 12/21/99 DSMC meeting (before 1st efficacy interim analysis) minutes, the DSMB statistician Dr. Lloyd Fisher stated that he was concerned that the committee would have a difficult decision to make if p = 0.005. It is not clear how this 0.005 level came up. The question is, were these observed p-values a part of guidance in selecting the 0.005 alpha level for the 2nd interim analysis?***

If yes, this may cause concern about potentially substantial inflation of total alpha level, particularly if such a strategy is practiced frequently throughout the trial. It is impossible for the reviewer to know how and whether the change of alpha spending function was affected indirectly as a result of seeing the results of the 1st interim analysis. Therefore, it is very difficult for the reviewer to assess the level of statistical significance even for the primary endpoint. This is also complicated by the fact that death/MI at 48 hours instead of the

primary endpoint was used in comparison with the alpha spending rule. To assess the potential impact of the possible data-dependent alpha reallocation for the single endpoint (say, death/MI at 48 hours) assuming that this endpoint is a priori designated for interim analysis (this was not the case, more discussions later), this reviewer conduct simulation studies according the following plans:

Scenario 1 (planned p-value stopping rule) The trial will be stopped to declare a statistically significant finding at the interim analysis showing the nominal p-value is smaller than 0.0001.

Scenario 2 The trial will be stopped to declare a statistically significant finding at the 1st interim analysis when the nominal p-value is less than 0.0001 or at the 2nd interim analysis when the nominal p-value is less than 0.005.

Scenario 3 The trial will be stopped to declare a statistically significant finding if one of the following conditions is met:

1) the nominal p-value < 0.0001 at the 1st interim analysis
2) the nominal p-value ≥ 0.0001 but < 0.005 at the 1st interim analysis and the nominal p-value < 0.005 at the 2nd interim analysis
3) the nominal p-value ≥ 0.005 at the 1st interim analysis and the nominal p-value < 0.0001 at the 2nd interim analysis

In Scenario 2, one changes the nominal alpha from 0.0001 to 0.005 for the 2nd interim analysis regardless of the nominal p-value of the 1st interim analysis, whereas in Scenario 3 the change occurs only when the nominal p-value of the 1st interim analysis is less than 0.005 but does not meet 0.0001 level.

The potential impact of alpha change could also depend on the timing of the interim analysis. Theoretically, one could make such a change, particularly like that in Scenario 3, immediately after one more patient contributes valid data. In ESPIRIT, the 1st interim analysis was performed approximately at the time that 1484 patients contributed data on 48-hour death/MI (this is about 62% information time) and the 2nd interim analysis is about 73% information time. After the 1st interim analysis, the DSMC decided to do the 2nd interim analysis in early February of 2000, only 3-4 weeks from the time of the 1st interim analysis, without specifying number of additional patients expected to contribute data or number of additional events expected during this period. Thus, there could have been a likelihood of no additional statistical information during this one-month period. That is, the 2nd interim analysis might have been performed at information time very close to 62%. Table 13 shows the total types I error

rate for the 1st and 2nd interim analyses under each scenario (based on 1,000,000 replication runs).

Table 13. Total type I error rate for 1st and 2nd interim analyses

Info time of 1st interim analysis	Info time of 2nd Interim analysis	Total type I error rate for 1st and 2nd interim analyses		
		Scenario 1	Scenario 2	Scenario 3
62%	73%	0.0001	0.0049	0.0026
62%	62%	0.0001	0.0051	0.0051

Since the primary efficacy endpoint was used as the main basis at the 1st interim analysis and death/MI at 48 hours was used at the 2nd interim analysis, there is a potential issue of multiplicity. From all the considerations described above, the true p-value for the primary efficacy endpoint may be less than a level of approximately 0.005 (= 0.0026 × 2) or 0.010 (= 0.0051 × 2), depending on the situation illustrated in Table 13. Regardless of which situation, the true p-value is statistically significant. The ESPIRIT results are internally very consistent.

4. CONCLUSION

The ESPIRIT results show with sufficient statistical evidence that eptifibatide gave a statistically significantly greater reduction of the composite events of death, MI, UTVR and TBO at 48 hours (the primary efficacy endpoint) than placebo in patients undergoing percutaneous coronary intervention with stent implantation. There was a statistically significantly greater reduction in the incidence of the key secondary endpoint, death, MI and UTVR at 30 days with eptifibatide. The results of adjudicated events show great internal consistency among different time points and among different endpoints. There was no great heterogeneity in the results of subgroups or geographical regions.

The investigator's reported events show much smaller effect of eptifibatide, which is not statistically significant.

/S/ 1/15/01

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Acting Team Leader

This review consists of 18 pages of text.

Concur: Dr. Chi 1/24/01

cc: NDA 20-718/S-010
HFD-110/Dr. Lipicky
HFD-110/Dr. Throckmorton
HFD-110/Ms. LoCicero
HFD-344/Dr. Barton
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/chron